Causes and risk factors of cerebral ischemic events in patients with atrial fibrillation treated with Non-vitamin K antagonist (NOACs) for stroke prevention: The ReNo Study

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Abstract

Background and Purpose: Despite treatment with oral anticoagulants patients with non-valvular atrial fibrillation (AF) may experience ischemic cerebrovascular events. The aims of this case–control study in patients with AF were to identify the etiology of and the risk factors for cerebrovascular ischemic events occurring during non-vitamin K antagonists (NOACs) therapy for stroke prevention.

Methods: Cases were consecutive patients with AF who had acute cerebrovascular ischemic events during NOACs treatment. Controls were consecutive patients with AF who did not have cerebrovascular events during NOACs treatment.

Results: Overall, 713 cases [641 ischemic strokes and 72 TIAs; median age 80.0 years, Interquartile Range (IQR) 12; median NIHSS on admission 6.0 IQR 10] and 700 controls (median age 72.0 years, IQR 8) were included in the study. Recurrent stroke was classified as cardioembolic in 455 cases (63.9%) according to the A-S-C-O-D classification. On multivariable analysis, off-label low dose of NOACs (OR 3.18; 95% CI 1.95-5.85), atrial enlargement (OR 6.64; 95% CI 4.63-9.52), hyperlipidemia (OR 2.40; 1.83-3.16) and CHA_2DS_2VASc score (OR 1.72 for each point increase; 95% CI 1.58-1.88) were associated with ischemic events. Among the CHA_2DS_2VASc components, age was older and presence of diabetes, congestive heart failure and history of stroke or TIA more common in patients who had acute cerebrovascular ischemic events. Paroxysmal AF was inversely associated with ischemic events (OR 0.45; 0.33-0.61).

Conclusions: In patients with AF treated with NOACs who had a cerebrovascular event, mostly but not exclusively of cardioembolic etiology, off-label low dose, atrial enlargement, hyperlipidemia and high CHA_2DS_2VASc score were associated with increased risk of cerebrovascular events.

Introduction

Clinical trials on the prevention of stroke in patients with atrial fibrillation (AF) have consistently shown a benefit associated with oral anticoagulant therapy. Despite an adequate treatment with vitamin K antagonists, some patients with AF still suffer ischemic cerebrovascular events (1). Non-vitamin K antagonist oral anticoagulants (NOACs) are currently recommended as the preferred anticoagulant strategy for patients with non-valvular AF, given their more favorable risk benefit profiles over warfarin (2-4).

The aims of this multicenter case–control study in patients with AF on NOACs for stroke prevention were to identify the etiology of and the risk factors for cerebrovascular ischemic events which occurred during therapy with NOACs.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Causes and risk factors of cerebral ischemic events in patients with non-valvular atrial fibrillation treated with NOACs for stroke prevention (ReNo) was a multicenter unmatched case-control study performed between January 2016 and June 2018. Consecutive patients with AF who experienced an acute ischemic stroke and had been prescribed NOACs (dabigatran, apixaban, rivaroxaban or edoxaban) for stroke prevention were included in the study. These patients, identified as cases, were enrolled in 37 Stroke Units across Europe, North America and Asia. Controls were patients with AF who had been taking NOACs for stroke prevention for more than 1 month and did not suffer cerebrovascular events after the initiation of anticoagulant therapy. Controls were consecutive outpatients attending four European Anticoagulant Therapy Services [Torino (358 patients), Perugia (190 patients), Varese (94 patients), Kyiv (46 patients)], and three stroke unit follow-up services (12 patients).

Cases who had suspended anticoagulant therapy at least 24 h before the cerebrovascular event for any reasons and patients who did not guarantee compliance were excluded. To verify compliance, the patients and family members were asked how the prescribed anticoagulant was taken.

The study was approved by the pertinent institutional review boards, if required. Informed consent was obtained from all patients.

Risk factors

For cases and controls, data on known stroke risk factors were collected as following: age, gender, history of hypertension (blood pressure higher than 140/90 mmHg at least twice before acute stroke or already under treatment with antihypertensive drugs), history of diabetes mellitus (fasting glucose level higher than 126 mg/dL pre-prandial on two examinations, glucose level higher than 200 mg/dL postprandial, or HbA1c higher than 6.5%, or under antidiabetic treatment), current cigarette smoking, hyperlipidemia (total cholesterol higher than 200 mg/dL or triglyceride higher than 140 mg/dL or already under lipid lowering therapy), history of symptomatic ischemic heart disease (myocardial infarction, history of angina or previous diagnosis of multiple lesions on thallium heart isotope scan or evidence of coronary disease on coronary angiography), history of symptomatic peripheral arterial disease (intermittent claudication of presumed atherosclerotic origin; or ankle/arm systolic blood pressure ratio lower than 0.85 in either leg at rest, or history of intermittent claudication with previous leg amputation, reconstructive surgery, or angioplasty), alcohol abuse (more than 300 g per week), obesity (body mass index higher than 30 kg/m^2), or previous stroke/TIA. Likewise, baseline variables were obtained for all patients including creatinine clearance (calculated by Cockcroft-Gault equation), type and duration of NOAC treatment. The doses of NOACs were recorded and the reasons for prescribing low doses were also collected. Low doses of NOACs were considered off-label in the absence of the recommended clinical and laboratory criteria for dose reduction (5-8). Low dose of dabigatran was considered as labelled for elderly patients (age ≥80 years), patients with moderate renal impairment (creatinine clearance 30–49 mL/min) and those with concomitant use of interacting drugs (e.g., verapamil). Low dose of rivaroxaban was considered as labelled for patients with moderate or severe renal impairment (creatinine clearance 15–49 mL/min). Low dose apixaban was considered as labelled for patients with at least two of the following: age ≥80 years, weight ≤60 kg, or serum creatinine ≥1.5 mg/dL. Low dose edoxaban was considered label in patients with moderate or severe renal impairment (creatinine clearance 15–49 mL/min), in those with concomitant use of interacting drugs and in those with a weight ≤60 kg.

Non-valvular AF was classified as: 1) paroxysmal: associated with episodes terminating spontaneously within seven days; 2) persistent: associated with episodes lasting more than seven days or requiring pharmacological and/or electrical cardioversion; 3) permanent: persisting for more than one year, either

because cardioversion failed or was not pursued (9). For the purpose of the present study, AF was classified into two types: paroxysmal or sustained (persistent or permanent).

For cases, the CHA_2DS_2VASc score (2 points for history of stroke or age older than 75 years and 1 point each for congestive heart failure, hypertension, diabetes, vascular disease, age between 65 to 74 years and female sex) was calculated before the cerebrovascular event. For controls, the CHA_2DS_2VASc score was calculated at the time of anticoagulant therapy initiation.

A trans-thoracic echocardiogram (TTE) was performed within 7 days from stroke onset in cases and during follow up in controls by a local cardiologist using a standardized protocol. Patients were imaged in the left lateral decubitus. Images were obtained using a 3.5 MHz transducer, at a depth of 16 cm in the parasternal (standard long- and short-axis images) and apical views (standard long-axis, two- and four- chamber images). Standard two-dimensional and color Doppler data, triggered to the QRS complex, were saved in cine loop format. Pulsed and continuous wave Doppler data were also stored digitally. Left atrial enlargement was defined following the American Society of Echocardiography guidelines and the European Association of Echocardiography (10,11).

Characteristics of patients with acute stroke or TIA during NOACs treatment

On admission, in all cases with acute ischemic stroke or TIA, stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS). A non-contrast cerebral computed tomography (CT) or cerebral magnetic resonance imaging (MRI) scan was performed on admission in all patients to exclude intracranial hemorrhage. All patients underwent angio-CT or MRI scan to assess intracranial stenosis and an ultrasonography examination of the carotid and vertebral arteries (12-14). Occlusion of an artery in the territory of the infarct was defined as an absence of flow and the presence of a visible plaque. For the latter, the occlusion was considered to be atherosclerotic.

For the causes of stroke, the A-S-C-O-D classification was used (15,16). A-S-C-O-D phenotyping (A: atherosclerosis; S: small-vessel disease; C: cardiac pathology; O: other causes; D: dissection) assigns a degree of likelihood of causal relationship to every potential disease (1 for potentially causal, 2 for causality is uncertain, 3 for unlikely causal but the disease is present, 0 for absence of disease, and 9 for insufficient

workup to rule out the disease) commonly encountered in ischemic stroke describing all underlying diseases in every patient.

White matter changes [leukoaraiosis defined on the first CT (or MR) examination as ill-defined and moderately hypodense (or hyperintensity on T2-weighted on MR) areas larger than 5 mm according to published criteria] were investigated (17). Leukoaraiosis in the deep white matter was dichotomized into absent versus present.

Statistical analysis

The aims of the unmatched analyses were to identify predictors of ischemic events. Univariate tests ($\chi 2$ test or Fisher's exact test with Yate's correction when appropriate) were used to compare patients with ischemic events (cases) with controls, regarding risk factors for stroke. Multivariable logistic regression analysis was performed to identify independent predictors for ischemic events. The variables included in this latter analysis were: CHA_2DS_2VASc score (separately as a continuous variable or including the risk factors within the score excluding the CHA_2DS_2VASc score), hyperlipidemia, alcohol abuse, paroxysmal AF, atrial enlargement and dose of NOACs. The variables low dose and off-label low dose were inserted into the multivariable model separately. Moreover, a sensitivity analysis after matching for age was performed. Data were analyzed with the SPSS/PC Win package 25.0.

Sample size calculation.

For this unmatched case-control study, it was assumed that at least 15% of controls would have had the risk factor with the lower incidence. In order to detect a minimum odds ratio of 1.5 with a power of 80% and an alpha risk of 5%, it was calculated that a total of 1,308 patients would have been needed (ratio controls/cases 1:1) (18).

Results

Characteristics and causes of cerebrovascular events occurring during anticoagulant therapy

During the study period, 713 consecutive patients on NOACs were admitted for an acute cerebrovascular event (641 ischemic strokes and 72 TIAs). The median age of these patients was 80.0 years, Interquartile Range (IQR) 12 and median NIHSS on admission was 6.0, IQR 10. Atherosclerotic lesions were detected in

420 patients (58.9%): extracranial ICA stenosis 30-49% in 190 (26.6%), extracranial ICA stenosis ≥50% in 95 (13.3%), vertebral/basilar artery stenosis ≥50% in 33 (4.6%), intracranial stenosis in the anterior circulation 30-49% in 26 (3.6%), intracranial stenosis in the anterior circulation ≥50% in 41 (5.7%) and stenosis in more than one location in 38 patients (5.3%). Leukoaraiosis was found in 404 patients (56.7%). The index event occurred after an average of 14.4 months from initiation NOACs.

Concerning the causes of the index events, 455 (63.9%) were considered cardioembolic strokes, according to A-S-C-O-D classification (Table 1).

Predictors of cerebrovascular ischemic events during anticoagulant therapy

The 713 cases were compared to a control group of 700 controls (median age 72.0 years, IQR 8). The characteristics of cases and controls are summarized in Table 2.

On univariable analysis, cases with ischemic events were older, had a higher prevalence of vascular risk factors and atrial enlargement on TTE. Among the cases, 317 (44.5%) were treated with low doses of NOACs compared to 207 (29.6%) of controls. Of the 317 cases treated with low doses, 111 (35.0%) were treated with off-label low doses compared to 53 of the 207 controls (27.5%) treated with off-label low dose. Of the 111 cases treated with off-label low dose, 38 were treated with low dose because of "fear" of bleeding, 10 had history of bleeding, 7 were prescribed concomitant antiplatelet therapy and 46 for other causes (cost of the drug, recurrent falls, amyloid angiopathy, anemia, history of cancer, age, misinterpretation of the patient, preference of the patient, gastro-intestinal discomfort and hypertension); in 10 patients, the cause remains unknown. Of the 53 controls treated with off-label low dose, 6 were treated with off-label low dose because of "fear" of bleeding, 10 had history of bleeding, 6 were prescribed concomitant antiplatelet therapy and 31 for other causes (recurrent falls, amyloid angiopathy, anemia, history of tumor, age, misinterpretation of the patient, preference of the patient, gastro-intestinal discomfort and hypertension).

The results of multivariable and the sensitivity analyses are reported in Table 3. Patients treated with off-label low doses and the presence of atrial enlargement, especially when severe, had a higher risk of ischemic events (OR 3.18; 95% CI 1.95-5.85, p=0.0001 and OR 6.64; 95% CI 4.63-9.52, p=0.0001, respectively).

Additionally, CHA_2DS_2VASc score was associated with the occurrence of ischemic events (OR 1.72 for each point increase; 95% CI 1.58-1.88, p=0.0001).

The characteristics of the patients with cerebrovascular events treated with low doses are summarized in Table 4. On multivariable analysis, CHA_2DS_2VASc score was associated with prescription of low dose NOACs (OR 1.35 for each point increase; 95% CI 1.20-1.52, p=0.0001). Low clearance of creatinine was associated with prescription of low dose NOACs (OR 0.98 for 1 ml/min increase; 95% CI 0.97-0.99, p=0.001).

Discussion

This unmatched case–control study showed that the main risk factor associated with an increased risk of ischemic cerebrovascular events was the administration of a low dose of NOACs. Specifically, 40-45% of the patients with ischemic events had been prescribed reduced doses of NOACs, and about 35% of these had been prescribed reduced off-label doses. The prescription of low dose was associated with higher CHA_2DS_2VASc score. The ORBIT II AF study reported that 1 in 7 patients treated with a NOAC were prescribed with a reduced dose of NOACs. Notably, more than half of the NOAC reductions were inconsistent with Food and Drug Administration (FDA) or European Medicines Agency (EMA) labeling and appeared to be unexplainably in patients with lower bleeding risk. In unadjusted analyses, patients receiving reduced NOAC doses had high crude adverse event rates, particularly those who should have received standard NOAC dosing. Although these results were consistent in adjusted analyses, the differences were not statistically significant (19).

In the ReNo study, about 30% of the patients with cerebrovascular events had stroke due to causes other than cardio-embolism. Indeed, ischemic stroke in patients with AF is not thought to be exclusively cardiogenic. For this reason, in patients with stroke during anticoagulation therapy, the first step should be to confirm the etiology of the new event that more than often requires adjustments of the original treatment strategy.

The presence of hyperlipidemia and the type of AF were independently associated with risks of cerebrovascular events in this study. Currently, these two variables are not represented in any international guideline risk scores for stroke in patients with AF. Therefore, it is plausible that by adding these two variables to currently used scores better predictions of risk could be obtained.

The ReNo study has the following limitations: 1) it was observational, and neither individual NOAC or their doses were randomized; 2) other pharmacological treatments besides NOACs were not investigated. Interactions between NOACs and other drugs are reported to be much lower than that of warfarin. Specifically, all currently available NOACs are substrates of the P-glycoprotein transporter, one-third of rivaroxaban is metabolized by the liver via CYP3A4/CYP3A5 and CYP2J2-dependent pathways and apixaban which has predominant non-renal clearance is eliminated via the CYP3A4, CYP1A2 and CYP2J2-dependent pathways. Therefore, it is plausible that drug interactions may have interfered with the anticoagulant effect; 3) we excluded patients who could not guarantee adherence to the prescribed treatment regimen. As this information was provided by the patients themselves or the care-giver, a laboratory assessment of the anticoagulant status during the event might have been informative (20,21); 4) we did not collect data regarding any possible off-label overdose of NOACs; which has been reported in literature to be about 3% (22); 5) the bleeding risk of the patients included in the ReNo study remained unknown;
6) Cases were collected from a number of Stroke Units in Europe, United States and Asia. Unfortunately, not all participating Stroke Units have an associated anticoagulant unit where the cases could have been collected. For this reason, we collected control data in 7 centers, all except one, associated to a Stroke Unit.
The strengths of our study include its adequate sample size and its prospective design. Additionally, our analyses reflect real-life experiences and thus, may provide valuable information that could significantly reduce the incidence of ischemic events in patients with AF and stroke during NOAC therapy.
Conclusion: In patients with AF treated with NOACs who had a cerebrovascular event, mostly but not exclusively of cardioembolic etiology, off-label low dose, atrial enlargement, hyperlipidemia and high CHA_2DS_2VASc score were associated with increased risk of cerebrovascular events.

Disclosures

Maurizio Paciaroni received honoraria as a member of the speaker bureau of Aspen, Sanofi-Aventis, Boehringer Ingelheim, Bayer, Bristol Meyer Squibb, Daiiki Sankyo and Pfizer.

Giancarlo Agnelli received honoraria as a member of the speaker bureau of Boehringer Ingelheim and Bayer.

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Stefan T. Engelter has received funding for travel or speaker honoraria from Bayer, Boehringer Ingelheim and Daiichi-Sankyo. He has served on scientific advisory boards for Bayer, Boehringer Ingelheim, BMS/Pfizer, and MindMaze and on the editorial board of Stroke. He has received an educational grant from Pfizer, and research support from Daiichi-Sankyo, compensation from Stago for educational efforts and research support from the Science Funds [Wissenschaftsfonds] of the University Hospital Basel, the University Basel, the "Freiwillige Akademische Gesellschaft Basel", the Swiss Heart Foundation, and the Swiss National Science Foundation.

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Francesco Corea reports expenses for meeting from Novartis.
Danilo Toni received honoraria as a member of speaker bureau from Boehringer Ingelheim, Bayer, Pfizer and Daiichi Sankyo. He received consultant honoraria as advisory board of Boehringer Ingelheim, Pfizer, Bristol Meyer Squibb, Daiichi Sankyo and Bayer.
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Table 1: The etiology of cerebrovascular events in patients on NOACs for stroke prevention

Etiology of stroke	ASCOD classification		
Cardioembolic (CE)	[A(0,2,3)-S(0,2,3)-C1-O(0,2,3)]	455	63.9%
Other possible causes		233	32.7%
Large Artery Disease (LAD)	[A1,S(0,2,3)-C(2,3)-O(0,2,3)]	24	3.3%
Small Vessel Disease (SVD)	[A(0,2,3)-S1-C(2,3)-O(0,2,3)]	74	10.4%
Other Causes (Other)	[A(0,2,3)-S(0,2,3)-C(2,3)-O1]	29	4.1%
CE and LAD	[A1-S(0,2,3)-C1-O(0,2,3)]	65	9.1%
CE and SVD	[A(0,2,3)-S1-C1-O(0,2,3)]	29	4.1%
CE and Other	[A(0,2,3)-S(0,2,3)-C1-O1]	5	0.7%
CE and LAD and SVD	[A1-S1-C1-O(0,2,3)]	3	0.4%
LAD and SVD	[A1-S1-C(2,3)-O(0,2,3)]	4	0.6%
ASCOD not collected		24	3.4%
Total		713	100%

Table 2. Characteristics of the cases and controls

	Cases (n=713)	Controls (n=700)	P
Age (years), mean (median)	78.1±9.1 (80.0)	71.3±11.3 (72.0)	0.0001
Females	375 (52.6%)	256 (36.6%)	0.0001
Duration of therapy (mean, months)	14.4±12.0	29.1±21.0	0.0001
Apixaban	221 (31.0%)	223 (31.8%)	0.7
Dabigatran	199 (27.9%)	160 (22.8%)	0.03
Edoxaban	43 (6.0%)	26 (3.8%)	0.04
Rivaroxaban	250 (35.1%)	291 (41.6%)	0.01
Low dose NOACs	317 (44.5%)	207 (29.6%)	0.0001
Non-label low dose	111/317 (35.0%)	53/207 (25.6%)	0.03
Creatinine clearance, mean (median)	66.5±25.1 (63.0)	76.3±25.9 (76.0)	0.0001
CHA_2DS_2VASc score≥4	607 (85.1%)	318 (45.4%)	0.0001
Hypertension	608 (85.3%)	562 (80.3%)	0.01
Diabetes Mellitus	203 (28.5%)	120 (17.1%)	0.0001
Hyperlipidemia	387 (54.3%)	192 (27.4%)	0.0001
Alcohol abuse	101 (14.2%)	118 (16.8%)	0.01
Current smoker	132 (18.5%)	116 (16.6%)	0.2
Congestive heart failure	223 (31.3%)	148 (21.1%)	0.0001
History stroke/TIA	339 (47.5%)	173 (24.7%)	0.0001
Myocardial infarction	174 (24.4%)	148 (21.1%)	0.1
Peripheral artery disease	123 (17.2%)	41 (5.9%)	0.0001
Paroxysmal AF	177 (24.8%)	289 (41.3%)	0.0001
Atrial enlargement on TTE	509/607 (83.9%)	154/431 (35.7%)	0.0001
Moderate	125/607 (20.6%)	44/431 (10.2%)	
Severe	168/607 (27.7%)	18/431 (4.2%)	

Table 3: Multivariable and sensitivity analyses: predictive factors for ischemic stroke or TIA

	OR (95% CI)	p	Sensitivity analysis OR (95% CI)	p
Low dose NOACs	1.23 (0.93-1.65)	0.1	1.09 (0.72-1.63)	0.6
Non-label low dose	3.18 (1.95-5.85)	0.0001	3.56 (1.72-7.37)	0.001
Hyperlipidemia	2.40 (1.83-3.16)	0.0001	2.82 (1.93-4.11)	0.0001
Alcohol abuse	0.90 (0.62-1.30)	0.5	0.92 (0.57-1.48)	0.7
Current smoker	1.19 (0.84-1.69)	0.3	1.25 (0.77-2.02)	0.4
Paroxysmal AF	0.45 (0.33-0-61)	0.0001	0.37 (0.25-0.54)	0.0001
CHA_2DS_2VASc score	1.72 (1.58-1.88)	0.0001	1.31 (1.16-1.48)	0.0001
Age	1.09 (1.07-1.10)	0.0001		
Females	1.31 (0.99-1.73)	0.054		
Hypertension	0.83 (0.57-1.20)	0.3		
Diabetes Mellitus	1.80 (1.30-2.40)	0.0001		
Congestive heart failure	1.45 (1.06-1.93)	0.02		
History stroke/TIA	1.48 (1.12-1.96)	0.006		
Vascular disease (myocardial infarction and/or peripheral arterial disease)	0.88 (0.65-1.19)	0.4		
In patients with TTE (n=1034):				
Atrial enlargement (yes/no)	6.64 (4.63-9.52)	0.0001	4.05 (2.75-5.95)	0.0001
No atrial enlargement	1 (Ref.)	0.0001		
Mild atrial enlargement	4.29 (2.71-6.77)			
Moderate atrial enlargement	8.06 (4.80-13.53)			
Severe atrial enlargement	23.28 (12.58-43.07)			

Table 4. Characteristics of the patients with cerebrovascular events treated with low dose of NOACs

	Low dose (n=317)	Standard dose (n=396)	p
Age (years), mean (median)	81.9±8.6 (82.0)	75.3±8.8 (76.0)	0.0001
Females	200 (63.1%)	171 (43.2%)	0.001
Creatinine clearance, mean (median)	57.3±23.7 (55.0)	70.7±23.5 (67.0)	0.0001
CHA_2DS_2VASc score≥4	293 (92.4%)	314 (79.3%)	0.0001
Hypertension	279 (88.0%)	329 (83.1%)	0.1
Diabetes Mellitus	94 (29.6%)	109 (27.5%)	0.5
Hyperlipidemia	161 (50.8%)	226 (57.1%)	0.08
Alcoholism	34 (10.7%)	67 (16.9%)	0.01
Current smoker	39 (12.3%)	93 (23.5%)	0.0001
Congestive heart failure	105 (33.1%)	120 (31.5%)	0.5
History of stroke/TIA	155 (48.9%)	183 (46.2%)	0.6
Myocardial infarction	112 (35.3%)	138 (43.8%)	1.0
Peripheral artery disease	43 (13.6%)	81 (20.4%)	0.02
Paroxysmal AF	141 (44.5%)	148 (37.4%)	0.1
Leukoaraiosis	200 (63.1%)	205 (51.8%)	0.001